Keeping Cell Suicide in Check

For most of human history, and even now, we have treated the sick with medicines whose mechanisms of action are a mystery. One such case is TNF-related apoptosis-inducing ligand (TRAIL), a protein we produce naturally as a regulator of programmed cell death (apoptosis) that is also administered as an effective cancer therapy. A better understanding of how TRAIL activates apoptosis preferentially in cancer cells could lead to further improvements in cancer therapies. To that end, Stéphanie Solier, Pharm.D., Ph.D., a Postdoctoral Fellow in the Laboratory of Molecular Pharmacology at CCR, and Yves Pommier, M.D., Ph.D., who heads the lab, describe new insights into TRAIL's mechanism of action in the January 2009 issue of Molecular and Cellular Biology.

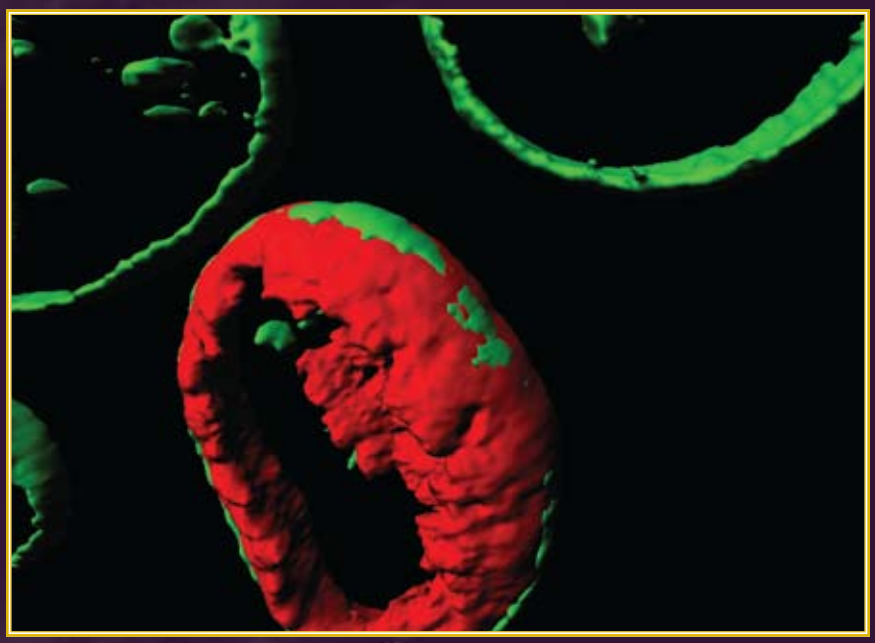
In normal cells, apoptosis can be activated in two ways: by direct damage within the cell or by an external pathway that is activated when certain signaling proteins bind to the cell's surface receptors and engage a death-inducing signaling complex. Although we know that TRAIL activates the latter system, the researchers proposed that TRAIL could also be utilizing components of the DNA damage response (DDR) pathway to destroy cancer cells. To test their hypothesis, they monitored the effects of TRAIL on specific proteins in cultured cancer cells. Two key findings emerged.

TRAIL was found to activate Chk2, a protein involved in the regulation of checkpoints used by cells to determine whether DNA damage is serious enough to proceed with programmed cell death. Drs. Solier and Pommier showed that activation of Chk2 amplifies apoptotic signaling and approximately doubles the number of dying cells that otherwise survive TRAIL treatment.

Whether it leads to apoptosis or not, DNA damage also induces modifications to histone proteins—key regulators of DNA structure and function—including phosphorylation of the histone H2AX (γ-H2AX) that can be visualized using a specific antibody developed by William Bonner, Ph.D., in the Laboratory of Molecular Pharmacology at CCR. Whereas DNA damage activates γ-H2AX locally in the nucleus, TRAIL induces an initial ring of γ-H2AX along the entire periphery of the nucleus that precedes apoptotic nuclear fragmentation.

In the June 2009 issue of *Cell Cycle*, Drs. Pommier and Solier followed up on this intriguing difference in histone modifications, proposing a previously unrecognized histone phosphorylation signature for apoptosis and demonstrating how this signature, together with the γ-H2AX ring, provides a new feature to monitor and study cell death. "The NCI recognized very early the value of γ-H2AX, and it has turned into an increasingly clinically useful biomarker," said Dr. Pommier.

These findings have many clinical implications for the treatment of cancer. The discovery that γ-H2AX activation by TRAIL uses segments of the DDR pathway provides a rationale for combining TRAIL and DNA-damage agents for anticancer therapy. It may also be possible to predict the effectiveness of TRAIL therapy based on the level of Chk2 in tumors, and activation of Chk2 in precancerous tumors may be able to prevent or delay cancer development.



(*Image: S. Solier, CCR*)

A representative 3-dimensional image of peripheral nuclear gamma-H2AX distribution in response to TRAIL *(gamma-H2AX is red and the nuclear envelope is green).*

To learn more about Dr. Pommier's research, please visit his CCR Web site at http://ccr.cancer.gov/staff/staff.asp?profileid=5812.